IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant : Masatoshi CHIBA

Group Art Unit: 1649

Serial No : 09/926,661

Examiner: Daniel E. KOLKER

Filed : February 28, 2002

For : LYOPHILIZED HGF PREPARATIONS

Commissioner for Patents
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REPLY BRIEF UNDER 37 C.F.R. § 41.41

This Reply Brief is in response to the Examiner's Answer mailed June 25, 2007, the period for reply extending until August 27, 2007 (August 25, 2007 being a Saturday). If any extension of time is necessary, this is an express request for any necessary extension of time and authorization to charge any required extension of time fee or any other fees, which may be required to preserve the pendency of the present application, to Deposit Account No. 19-0089.

Appellant notes that this Reply Brief is being filed under 37 C.F.R. § 41.41(a)(1) and is directed to the arguments presented in the Examiner's Answer, and therefore must be entered unless the final rejection is withdrawn in response to the instant Reply Brief. With regard to this Reply Brief, Appellant notes that it is addressing points made in the Examiner's Answer mailed June 25, 2007 and not repeating the arguments set forth in the Appeal Brief filed February 15, 2007.

Appellant respectfully submits that the Appeal Brief filed February 15, 2007 fully addresses the requirements for patentability of the pending claims. Accordingly, the present remarks are merely supplemental to the Appeal Brief field on February 15, 2007. In order to facilitate review of the Reply Brief and for the sake of brevity, the present remarks do not include a discussion of all rejected claims or points raised by the Examiner, and such is not to be

considered an acquiescence to the Examiner's rejections or remarks. Indeed, the present remarks focus solely on the Examiner's interpretation of a particular quoted phrase from Nakamura (European Application No. 0456188 A1), his reliance on which is the foundation of all of the outstanding rejections.

Prior to addressing the Examiner's comments in the Answer, for ease of reference, Appellant notes that independent claim 1 on appeal is directed to a lyophilized preparation comprising a hepatocyte growth factor, a stabilizing agent comprising arginine, lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof, for preventing formation of an aggregate of the hepatocyte growth factor, sodium chloride, and a buffering agent, which is prepared from an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL. Independent claim 3 adds the additional element that the preparation be capable of preparing an aqueous solution containing the hepatocyte growth factor at a concentration lower than 5 mg/mL by redissolution.

Turning to the Examiner's Answer, Appellant notes that the Examiner relies upon Nakamura et al. (European Application No. 0456188 A1, hereinafter "Nakamura") for all of his rejections, and his interpretation of the disclosure of this document is critical to sustaining his rejections. Stated very briefly, Appellant submits that Nakamura fails to disclose Appellant's claimed invention with sufficient specificity to support a rejection under 35 U.S.C. § 102. To arrive at Appellant's claimed subject matter from Nakamura, one must select and re-combine disclosures in a manner not intended by Nakamura. To the contrary, the Examiner contends that Nakamura discloses Appellant's claimed invention with sufficient specificity to establish a *prima facie* case of anticipation.

In the Examiner's Answer, the Examiner maintains all of the rejections, emphasizing his position that Nakamura specifically discloses all of the elements of the claimed invention. In support of his argument, the Examiner points out that Nakamura indicates that the disclosed elements, which Appellant maintains are not disclosed in the proper specific combination, "'*may be used alone or in combination.*'" (Page 4, first full paragraph, of the Examiner's Answer; Examiner's emphasis.) From this statement in Nakamura, the Examiner concludes that

> Nakamura teaches that any of the elements can be added either individually or in a combination, i.e. all of them can be combined. The *list to be added is relatively small* and *by stating that they can be combined, Nakamura teaches the combination of elements now claimed.*

(Id.; emphasis added.) Appellant respectfully submits that the Examiner's conclusion is not supported by Nakamura's statement.

The passage the Examiner relies upon for the quotation above is set forth in its entirety, as follows:

> The therapeutic agents for hepatocirrhosis of the invention may contain other additives such as stabilizers, excipients, dissolution-promoters, adsorption-preventors and antioxidants, and examples thereof include, for example, sugars such as mannitol and glucose, amino acids such as glycine, alanine, lysine and arginine, proteins such as albumin, alcohols such as ethylene glycol and glycerol, hydrophilic polymers such as polyethylene glycol, inorganic salts such as NaCl, organic salts such as sodium citrate, surfactants such as Polysorbate 80 and reducing agents containing sulfur, which may be used alone or in combination.

(Nakamura, column 9, line 52 – column 10, line 6.) The passage clearly states that the additives "may be used alone or in combination"; however, Appellant respectfully submits that the list is not small and that Appellant's claimed invention is not specifically taught. Moreover, when Nakamura's entire disclosure is considered, it is quite clear that Appellant's claimed invention is not specifically shown.

For example, Examples disclosed in Nakamura include Examples 1 – 5 of freeze-dried HGF preparations. However, in Examples 1 and 2, the buffer solution has a pH value of 7.4, while no amino acid is used for stabilization. In Examples 3 and 4, the aqueous solution does not contain a buffering agent. Only Example 5 discloses lyophilization of HGF with a solution comprising an amino acid (glycine). However, the solution of Example 5 is not buffered and does not contain a salt. Thus, Nakamura's examples provide no further guidance about which additives, if any, can or should be added to a formulation.

Example 1 from Nakamura (column 14, lines 25-35), which the Office Actions had cited and relied upon, shows, in addition to the HGF, phosphate buffer, NaCl, human serum albumin,

and Polysorbate 80. But it does not contain arginine, or any of the other amino acids required by Appellant's claims: lysine, histidine, glutamine, proline, glutamic acid, or aspartic acid, or a pharmacologically acceptable salt thereof. Nakamura specifically included certain "additives" (as listed above from Nakamura, column 9, line 52 – column 10, line 6) in Example 1 – human serum albumin and Polysorbate 80 – but it did not include arginine (or any other recited amino acid). There is no teaching or suggestion in Nakamura as to any desirability to add any other ingredient in the Example 1 composition.

Moreover, the list of other additives referenced by the Examiner is merely a list of exemplary optional ingredients with a broad generalization of the type of additives. There is no mention of the desirability of combining any of the members of this broad list of ingredients to achieve any desired outcome. For this reason as well, Nakamura cannot be said to disclose Appellant's claimed invention.

Still further, Appellant notes that a *prima facie* case of obviousness cannot be made from Nakamura for at least the following reasons. As noted above, the specific Examples disclosed by Nakamura do not include arginine. Moreover, there is nothing in Nakamura that would cause one of ordinary skill in the art to add arginine, or to replace another component of Nakamura's Examples with arginine. There is no suggestion of its desirability as an additional additive, and thus, there is no reason one of skill in the art would add it to Nakamura's exemplified compositions. Additionally, there is no suggestion of its interchangeability with some other component already present in one of Nakamura's compositions. For these reasons, there is no reason that a person of skill in the art would select, from all of the choices of "additives" in Nakamura, arginine. There is no teaching or suggestion in Nakamura to arrive at Appellant's claim.

Additionally, there is not a reasonable expectation of success in a modification of Nakamura that would result in the presently claimed invention. Appellant respectfully refers the Board to the "Background Art" section of the present specification, which describes at least two published HGF formulations, examples of which are described as including, for example, human serum albumin, mannitol, lysine, arginine, glycine, and alanine, as stabilizing agents. However,

each of these formulations is described as being unacceptable: one for lack of long-term stability, and the other for being undesirable for human administration. It is respectfully submitted that modifying or changing the additives in HGF formulations can result in unexpected results and undesirable final products. Without more, there is no reasonable expectation of success in a modification of Nakamura.

In summary, Appellant respectfully submits that while Nakamura discloses compositions of HGF, it does not disclose Appellant's claimed subject matter. Nakamura's compositions are different from those claimed by Appellant, and the statement in Nakamura that additives "may be used alone or in combination" is not an invitation to create compositions that Nakamura did disclose. Appellant respectfully submits that Nakamura et al. fails to specifically disclose or suggest Appellant's claimed invention, and the Examiner has failed to make out a *prima facie* case of anticipation and obviousness.

In closing, Appellant respectfully submits that each and every pending claim of the present application meets requirements for patentability, and that the present application and each pending claim are allowable over the prior art of record.

Respectfully submitted,
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